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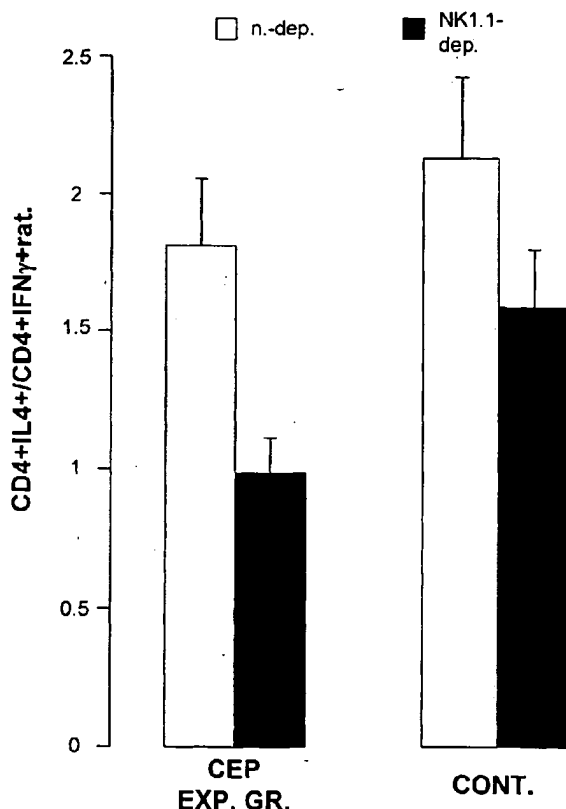
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- (71) Applicant (for all designated States except US): **HAD-ASIT MEDICAL RESEARCH SERVICES AND DEVELOPMENT LTD.** [IL/IL]; P.O. Box 12000, 91120 Jerusalem (IL).
- (72) Inventor; and  
(75) Inventor/Applicant (for US only): **ILAN, Yaron** [IL/IL]; 4/5 Yehoshua Bitzur Street, 96347 Jerusalem (IL).
- (74) Agents: **LUZZATTO, Kfir et al.**; Luzzatto & Luzzatto, P.O. Box 5352, 84152 Beer-Sheva (IL).
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(54) Title: **EDUCATED NK T CELLS AND THEIR USES IN THE TREATMENT OF IMMUNE-RELATED DISORDERS**



(57) Abstract: The present invention relates to a method for the treatment of immune-related disorders in a mammalian subject in need of such treatment. This method comprises the step of manipulating the NK T cell population in said subject by suitable means, said manipulation of the NK T cell population resulting in modulation of the Th1/Th2 balance toward anti-inflammatory cytokine producing cells. Manipulation of the NK T cell population may be performed either by depletion of said cells by a suitable means or alternatively by *ex vivo* education of the NK T cells, such that the educated NK T cells have the capability to modulate the Th1/Th2 balance toward anti-inflammatory cytokine producing cells. The invention further relates to pharmaceutical compositions for the treatment of immune-related disorders in a mammalian subject. These compositions comprising as an effective ingredient an *ex vivo* educated NK T cell. The invention further provides for an *ex vivo* educated NK T cell and uses thereof in the treatment of immune-related disorders.

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/IL 01/01197

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K38/19

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, WPI Data, PAJ, MEDLINE, CHEM ABS Data, SCISEARCH

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>TROP S ET AL: "LIVER-ASSOCIATED LYMPHOCYTES EXPRESSING NK1.1 ARE ESSENTIAL FOR ORAL IMMUNE TOLERANCE INDUCTION IN A MURINE MODEL"</p> <p>HEPATOLOGY, WILLIAMS AND WILKINS, BALTIMORE, MD, US, vol. 29, no. 3, March 1999 (1999-03), pages 746-755, XP000990485</p> <p>ISSN: 0270-9139</p> <p>abstract; figures 2,5; table 1</p> <p style="text-align: center;">--- -/-</p>	1-55

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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- \* & \* document member of the same patent family

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax: (+31-70) 340-3016

Authorized officer

Novak, S

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International Application No

PCT/IL 01/01197

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ILAN YARON ET AL: "Treatment of experimental colitis by oral tolerance induction: A central role for suppressor lymphocytes." AMERICAN JOURNAL OF GASTROENTEROLOGY, vol. 95, no. 4, April 2000 (2000-04), pages 966-973, XP002199588 ISSN: 0002-9270 abstract; figures 1,2,4,7	1-55
X	BURDIN N ET AL: "IMMUNOZATION WITH ALPHA-GALACTOSYLCERAMIDE POLARIZES CD1-REACTIVE NK T CELLS TOWARDS TH2 CYTOKINE SYNTHESIS" EUROPEAN JOURNAL OF IMMUNOLOGY, WEINHEIM, DE, vol. 29, 1999, pages 2014-2025, XP002938932 ISSN: 0014-2980 abstract; figures 1-3,5,6	1-55
Y	SREDNI BENJAMIN ET AL: "Predominance of TH1 response in tumor-bearing mice and cancer patients treated with AS101." JOURNAL OF THE NATIONAL CANCER INSTITUTE (BETHESDA), vol. 88, no. 18, 1996, pages 1276-1284, XP002196802 ISSN: 0027-8874 the whole document	1-55
Y	US 5 721 351 A (LEVINSON DOUGLAS ADAM) 24 February 1998 (1998-02-24) the whole document	1-55
Y	US 6 066 498 A (LEVINSON DOUGLAS ADAM) 23 May 2000 (2000-05-23) page 36, column 1 -page 70, column 70	1-55
Y	GOTSMAN I ET AL: "Effect of peripheral immune tolerance on liver-associated lymphocytes expressing NK1.1." TRANSPLANTATION PROCEEDINGS, vol. 32, no. 4, June 2000 (2000-06), pages 749-750, XP002199589 Fifth Annual Congress of the Transplantation Society of Israel; Nazareth, Israel; June 02-05, 1999 ISSN: 0041-1345 the whole document	1-55
A	US 6 066 322 A (LEVINSON DOUGLAS ADAM) 23 May 2000 (2000-05-23) -/-	

## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/IL 01/01197

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	<p>SHLOMAI AMIR ET AL: "Immunomodulation of experimental colitis: The role of NKI. I liver lymphocytes and surrogate antigens: Bystander effect." JOURNAL OF PATHOLOGY, vol. 195, no. 4, November 2001 (2001-11), pages 498-507, XP002196803 ISSN: 0022-3417</p> <p>-----</p>	

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/IL 01/01197

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5721351	A	24-02-1998	US 6066322 A	23-05-2000
			AU 718245 B2	13-04-2000
			AU 5178396 A	23-09-1996
			CA 2214589 A1	12-09-1996
			EP 0813538 A1	29-12-1997
			JP 11501807 T	16-02-1999
			WO 9627603 A1	12-09-1996
			US 6066498 A	23-05-2000
			US 6204371 B1	20-03-2001
			US 6084083 A	04-07-2000
			US 6288218 B1	11-09-2001
			US 6156887 A	05-12-2000
US 6066498	A	23-05-2000	US 5721351 A	24-02-1998
			US 6066322 A	23-05-2000
			AU 718245 B2	13-04-2000
			AU 5178396 A	23-09-1996
			CA 2214589 A1	12-09-1996
			EP 0813538 A1	29-12-1997
			JP 11501807 T	16-02-1999
			WO 9627603 A1	12-09-1996
			US 6204371 B1	20-03-2001
			US 6084083 A	04-07-2000
			US 6288218 B1	11-09-2001
			US 6156887 A	05-12-2000
US 6066322	A	23-05-2000	AU 718245 B2	13-04-2000
			AU 5178396 A	23-09-1996
			CA 2214589 A1	12-09-1996
			EP 0813538 A1	29-12-1997
			JP 11501807 T	16-02-1999
			WO 9627603 A1	12-09-1996
			US 6066498 A	23-05-2000
			US 5721351 A	24-02-1998
			US 6204371 B1	20-03-2001
			US 6084083 A	04-07-2000
			US 6288218 B1	11-09-2001
			US 6156887 A	05-12-2000